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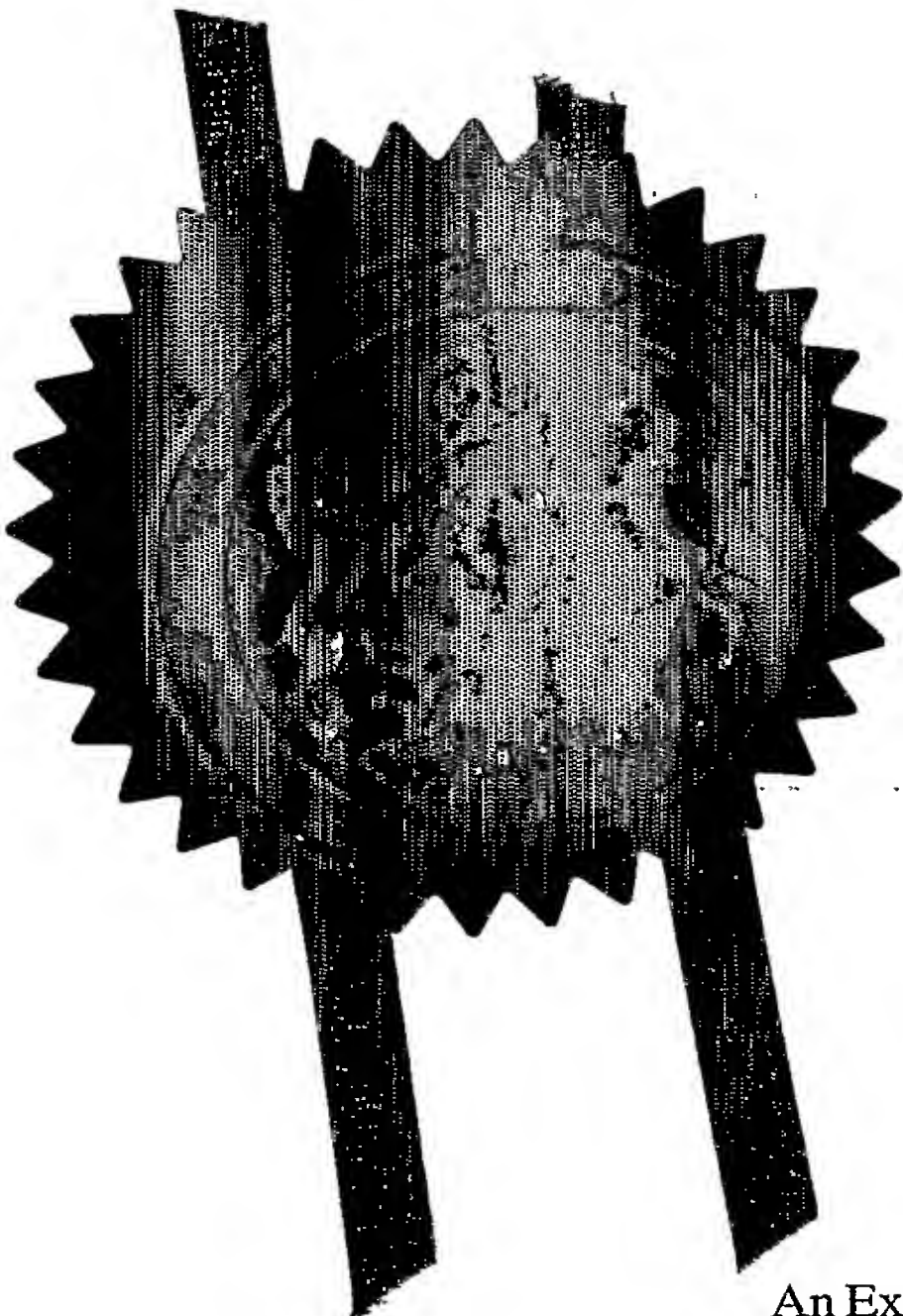
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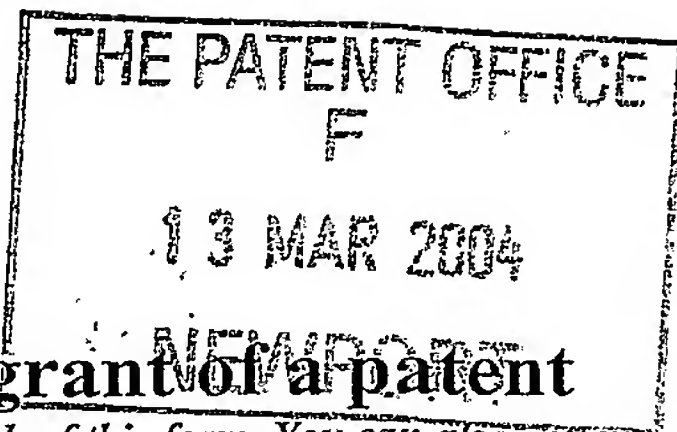
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1. Your reference 15836 MdH

13 MAR 2004

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2. Patent application number
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3. Full name, address and postcode of the or of each applicant (underline all surnames)

Accentus plc
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Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

England & Wales

8B2243003

4. Title of the invention Metal Implants

5. Name of your agent (if you have one)

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"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

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Number of earlier application

Date of filing
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

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Description	8
Claim(s)	1
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Statement of inventorship and right to grant of a patent (Patents Form 7/77)

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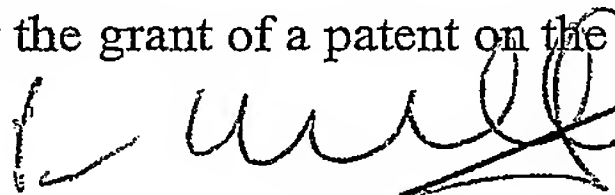
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11. Peter Turquand MANSFIELD (on behalf of Accentus plc by virtue of a Power of Attorney dated 18th February 2003)

I/We request the grant of a patent on the basis of this application.

Signature



Date 9th March 2004

12. Name and daytime telephone number of person to contact in the United Kingdom

Frances Esplin - 0870 1902911

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Metal Implants

This invention relates to metal implants for use in surgical procedures, and in particular to the
5 introduction of a biocidal material into such implants to suppress or control infection.

Various surgical procedures require the use of implants. For example cancerous bone may be removed, in
10 prosthetic surgery, to be replaced by a metal implant. Such an implant may for example be of titanium alloy, which is very strong and relatively light. To ensure a hard-wearing surface the provision of a titanium nitride coating has been suggested. There is furthermore a risk
15 of introducing infection when implanting such metal implants, and it has been suggested that metallic silver might be electroplated onto metal implants, the silver being a biocidal material that can control infection without causing toxic effects to the patient. However
20 such coatings, whether of titanium nitride or silver, may be undercut due to corrosion from body fluids, so that the coating may detach from the implant, which may can increase wear and cause tissue damage. WO 03/089023 describes a way of pretreating an implant by anodising at
25 10 V to form a phosphate layer, and then incorporating biocidal silver ions in this layer by ion exchange. A way of making a significantly improved layer has now been found.

30 According to the present invention there is provided a method of treating a metal implant for use in a surgical procedure, so as to form a surface layer that is integral with the metal substrate and which incorporates a biocidal material, wherein the method comprises
35 anodising the implant at a voltage above 50 V for a period of at least 30 min, so as to generate a surface

layer, and then performing ion exchange so as to incorporate ions of a biocidal metal into the surface layer.

5 The biocidal material should preferably be effective for at least 6 weeks, preferably for up to 6 months after surgery, and the release rate should be low to avoid toxic effects on body cells. Furthermore the total quantity of biocidal material is preferably also limited
10 to minimize any toxic effects. Performing the anodising at a voltage above 50 V has two effects: it initially generates a dense hard surface layer whose thickness is primarily determined by the voltage, and it then generates shallow pits in the surface which are filled
15 with a somewhat softer and more porous material. The absorption of biocidal metal ions is primarily into the material within the shallow pits, so that the total quantity of biocidal material and its release rate can be controlled by controlling the magnitude of the anodising
20 voltage and its duration, so as to control the number and size of the shallow pits. The anodizing might be carried out at a voltage as high as 500 V or 750 V, but more usually is performed between 50 V and 150 V. The duration may be up to 24 hours, but preferably no more than 12
25 hours, for example 2 hours or 6 hours.

It is also desirable if the surface is highly polished before production of the surface layer. This may for example be achieved by electropolishing. One
30 benefit of performing the anodising at a voltage in this significantly higher range is that the surface finish is not deleteriously affected; if the surface is polished before anodising so as to be shiny, then it will remain shiny after the high-voltage anodising step. This is in
35 contrast to the effect of low voltage anodising, which generates a milky or matt appearance at the surface.

In principle, a range of different materials may be used for the biocidal material. Gold, platinum and palladium would be potentially suitable, although
5 expensive; silver is preferable as it is not particularly soluble in body fluids due to the presence of chloride ions and the low solubility of silver chloride. Other elements such as copper, tin, antimony, lead, bismuth and zinc might be used as ions combined into the surface
10 layer. The rate of release would be controlled, in this case, primarily by the strength of the absorption of the metal ions in the layer.

The metals that may be used to make such prosthetic
15 implants are typically a form of stainless steel, a titanium alloy, or a cobalt/chromium alloy. The standard alloys for this purpose are titanium 90% with 6% aluminium and 4% vanadium (British standard 7252), or chromium 26.5-30%, molybdenum 4.5-7%, and the remainder
20 cobalt (British standard 7252 part 4).

Preferably the implant is initially polished to provide a very smooth surface. Both stainless steel (chromium/iron/nickel) and cobalt/chromium alloy can be
25 electro-polished using as electrolyte a mixture of phosphoric acid and glycerine, or a mixture of phosphoric acid and sulphuric acid. Titanium alloy can be electro-polished using acetic acid, or a mixture of nitric and hydrofluoric acids. Alternatively the implants might be
30 subjected to a combination of anodic passivation with mechanical polishing, which may be referred to as electrolinishing, this process removing the oxide that protects surface roughness, the surface at that point then being electrochemically re-passivated, so producing
35 a mirror-smooth finish. Various electrolytes are suitable for this purpose, including nitric acid mixed

with sulphuric acid, sodium hydroxide, sodium phosphate, or sodium hydroxide mixed with sodium nitrate.

After polishing the surface of the metal, surface
5 conversion can take place. A layer of metal oxide or phosphate is formed by anodising in a suitable electrolyte, so that the oxide or phosphate layer builds up at the surface of the metal, as described above. Biocidal metal ions can then be absorbed from an aqueous
10 salt solution into the oxide or phosphate matrix, for example the ions Ag^+ or Cu^{++} . Cations of palladium, platinum or even ruthenium could be absorbed in a similar way. If desired, deposited silver, platinum or palladium could then be converted to metal within the oxide or
15 phosphate surface coating, this reduction being performed chemically or electrochemically or by light.

The invention will now be further and more particularly described, by way of example only, and with
20 reference to the accompanying drawings in which:

Figure 1 shows a diagrammatic sectional view through part of the surface of an implant subjected to a low voltage anodising treatment;
25

Figure 2 shows a corresponding sectional view of an implant subjected to a high-voltage anodising treatment of the invention; and

30 Figure 3 shows the surface composition profile of a specimen treated as in figure 2, the profile being determined by secondary neutral mass spectrometry.

A hip implant is made of titanium alloy (Ti/Al/V).
35 The implant is cleaned ultrasonically using first acetone as the liquid phase, and then a 1 M aqueous solution of

sodium hydroxide, and is then rinsed in de-ionised water. The surface is initially shiny, with a pale grey colour. The cleaned implant is then immersed in a stirred 12% (weight) solution of phosphoric acid, and is anodized for 2 hours at a maximum voltage of 100 V and a maximum current of 10 mA/cm², so as to form a surface coating of titanium oxide and phosphate. Within a couple of minutes a dense dielectric layer is formed on the surface, and the current then adopts a stable low value for the rest of the anodising period. The surface forms a hard surface layer which can have different coloured appearances due to optical interference effects; during the initial stage of anodising, the surface colour varies from purple/blue, through blue, green, yellow, orange, and then finally red. Anodising at 100 V produces a film thickness of about 0.14 µm (140 nm). The anodised implant is then rinsed in de-ionised water again.

The implant is then immersed in a stirred 0.1 M aqueous solution of silver nitrate, and left for 2 hours. As a result of ion exchange there is consequently some silver phosphate in the titanium phosphate coating. The implant is then ready to be implanted. During exposure to body fluids there will be a slow leaching of silver ions from the phosphate layer, so that any bacteria in the immediate vicinity of the implant are killed. Infection arising from the implant is therefore suppressed.

Referring to figure 1, where anodising of a titanium implant 30 is performed at 10 V for 2 hours, the current falls to a low value over the first couple of minutes during anodising, but the current then rises again with the formation of a porous surface layer with 20 µm macropores and 1 µm micropores. This produces a porous high-surface-area layer 32 which is about 2 µm thick, of

hydrous titanium oxide and phosphate. This is highly effective at absorbing silver ions, and can provide an initial silver capacity of about 70-100 $\mu\text{g}/\text{cm}^2$; this is well below the toxic level, but more than adequate to
5 provide a biocidal effect.

Referring to figure 2, where anodising is performed at a high voltage such as 100 V for 2 hours, as mentioned above the current initially falls to a low value, and
10 then remains steady. The surface forms a hard anodised oxide layer 34 typically of thickness about 0.14 μm , but in which there are pits 36 typically of diameter about 5 μm and depth about 0.4 μm which are filled with titanium oxide as a result of hydrolysis from localised titanium
15 dissolution. Such pits 36 are approximately circular in plan, and make up between 15 and 20% of the surface area. Surface analysis techniques have confirmed that, after ion exchange treatment, the absorbed silver is associated with the titanium oxide/phosphate phase at the surface;
20 this is true for both the low voltage and the high-voltage anodising procedures. The high-voltage anodised surface absorbs silver to a small extent at the outer surface of the hard layer 34, and to a larger extent within the more porous material in the pits 36; overall
25 there is somewhat less initial capacity for silver, typically about 9 $\mu\text{g}/\text{cm}^2$. This is still sufficient to provide the required biocidal effect.

Thus the effects of anodising at 100 V for 2 hours
30 are to produce a hard and compact oxide layer whose thickness depends upon the voltage (the relationship being approximately 1.4 nm per volt) this film having a coloured appearances determined by the film thickness, and retaining the surface microstructure (e.g. polished
35 finish). Furthermore the surface is pitted, with pits about 0.3 μm deep filled with hydrous titanium dioxide

covering slightly less than a fifth of the surface. This can be loaded with silver at about $9 \mu\text{g}/\text{cm}^2$.

Measurements of the surface composition at different depths below the surface have been measured using secondary neutral mass spectrometry on a titanium alloy specimen treated as described above. The results are shown in figure 3, to which reference is now made. It will be observed that in the surface region, down to about $0.14 \mu\text{m}$ (marked by the broken line), the composition is about 73% oxygen and about 18% titanium, with phosphorus at about 6%; this corresponds to the hard surface layer 34. There is then a zone in which the titanium concentration increases and the oxygen concentration decreases, down to about $0.4 \mu\text{m}$; this corresponds to the depths at which there are pits containing titanium oxide. At greater depths the composition is evidently a titanium/aluminium alloy.

Measurements have also been made of the loss of silver from the surface of the anodised implant into a brine flowing over the surface (at a linear velocity of about $0.7 \text{ ml cm}^{-2} \text{ h}^{-1}$). The initial rate of silver release over the first 24 hours is about $0.1 \mu\text{g cm}^{-2} \text{ h}^{-1}$, the release rate then gradually falling over the next 24 hours to about half that value, then remaining steady for another 48 hours, before decreasing again. But throughout this period the concentration of silver in the leaching brine was sufficient to be biocidal.

30

The silver capacity can be adjusted in three ways. It may be changed by changing the number of pits, and this can be either by changing the voltage, or by changing the concentration of pitting agents (such as chloride or fluoride ions) which are present as impurities in the phosphate electrolyte. For example the

concentration of such monovalent ions can be decreased by a selective anion exchange treatment; or their concentration could be increased by adding appropriate acids. Alternatively the pits might be grown to larger
5 depths and diameters; this may be achieved by carrying out the anodising for a longer period of time.

It may also be appropriate to change the current density.

10

By anodizing at a higher voltage the thickness of the hard oxide layer can be increased, for example being about 0.7 μm at 500 V. Once this layer has been formed, as indicated by the decrease in the current, the voltage
15 might be changed. During this second stage the pits are formed, and gradually grow in size, and this may be carried out at a lower voltage.

20

Claims

1. A method of treating a metal implant for use in a surgical procedure, so as to form a surface layer that is
5 integral with the metal substrate and which incorporates a biocidal material, wherein the method comprises anodising the implant at a voltage above 50 V for a period of at least 30 min, so as to generate a surface layer, and then performing ion exchange so as to
10 incorporate ions of a biocidal metal into the surface layer.

2. - A method as claimed in claim 1 wherein the anodising is performed so as to generate a dense hard surface layer
15 and also shallow pits in the surface which are filled with a somewhat softer and more porous material, and wherein the magnitude of the anodising voltage and its duration are controlled, so as to control the number and size of the shallow pits.

20

3. A method as claimed in claim 1 or claim 2 wherein the implant is of a metal consisting primarily of titanium, and the biocidal metal is silver.

25

15836 MdH

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Chartered Patent Agent
Agent for the Applicant

30

Abstract

Metal Implants

5 A metal implant for use in a surgical procedure is
provided with a surface layer that is integral with the
metal substrate, and which incorporates a biocidal
material. The surface layer is grown by anodising at a
voltage between 50 and 150 V, and the biocidal material
10 incorporated in it by ion exchange. This produces a
significantly harder surface than anodising at low
voltage, and generates pits containing ion-absorbing
material.

15 15836 MdH

Fig. 1 (PRIOR ART)

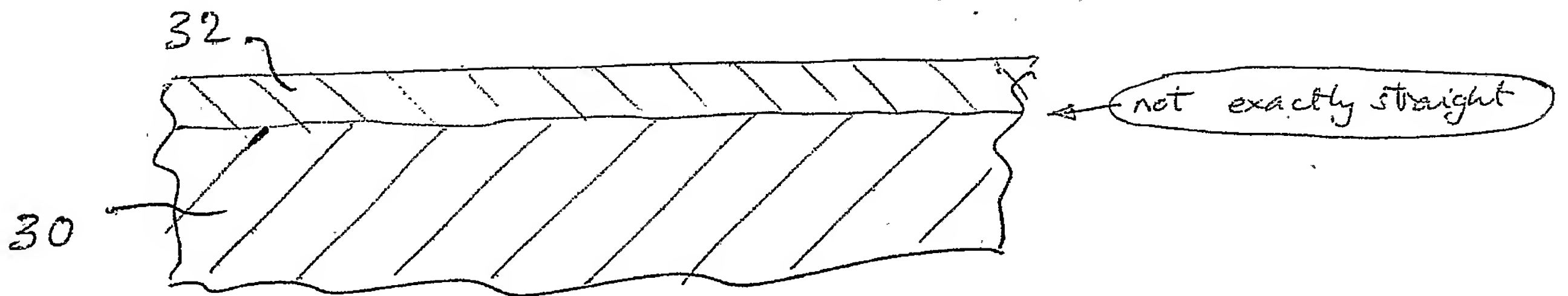


Fig. 2

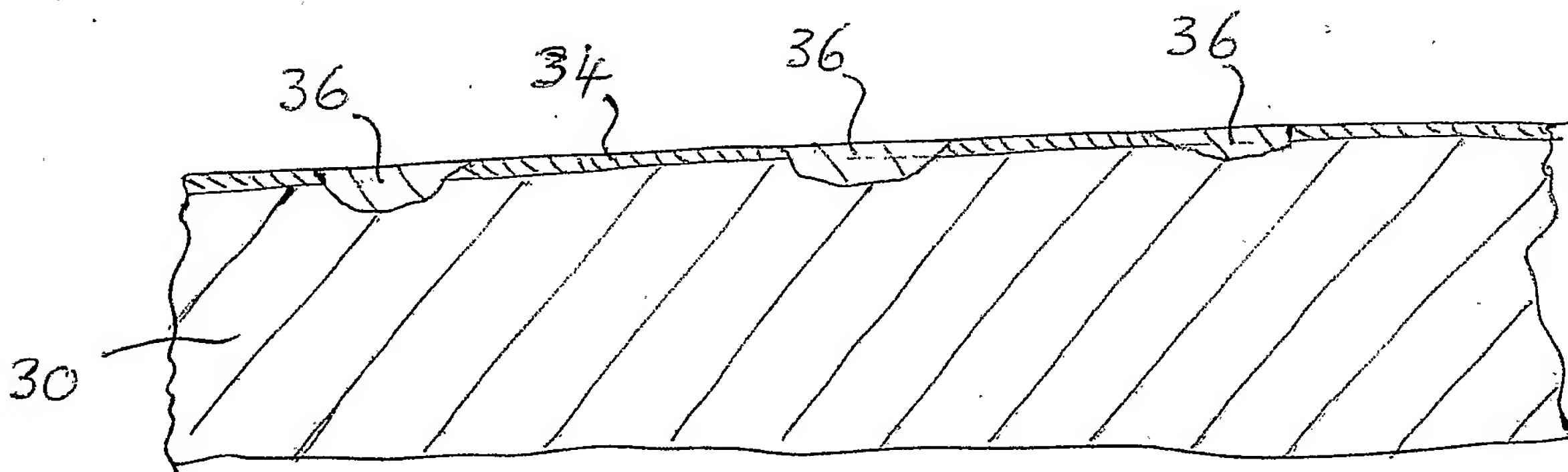
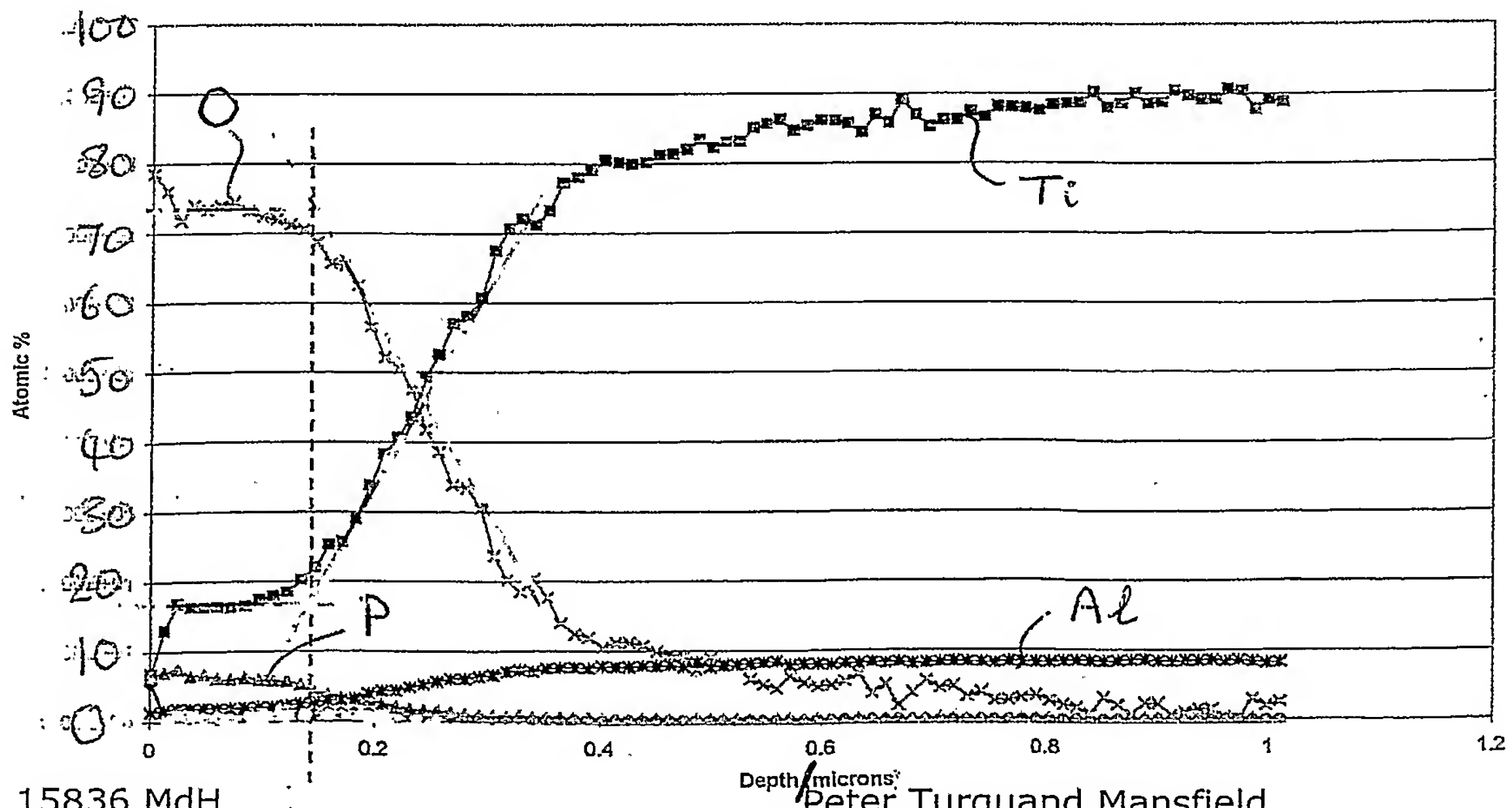


Fig. 3



15836 MdH

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